REMARKS

Drawing Replacement

According to the Office, Figure 22 includes unacceptable identifiers. However, it should be noted that Figure 22 is clearly explained on pages 6 and 7 of the application, and recreated below:

Figures 22 A-B show the effects of low doses of 4-APAA, 5-ASA, and both compounds on toxin A-induced (10 μg) colonic luminal fluid accumulation and MPO activity. Toxin A significantly stimulated luminal fluid accumulation and MPO activity and this was significantly inhibited by both compounds individually and by the combination of both compounds. However, the combination of both compounds inhibited significantly more toxin A-induced luminal fluid accumulation than either compound alone. Toxin A-induced MPO activity was significantly inhibited only by the combination of both 4-APAA and 5-ASA. The values shown are mean ± SEM; N = 3. * $P < 0.01$ vs. toxin A^-/4-APAA$^-$/5-ASA$^-$; ** $P < 0.001$ vs. toxin A^-/4-APAA$^-$/5-ASA$^-$; # $P < 0.05$ vs. toxin A^+; ## $P < 0.01$ vs. toxin A^+; ### $P < 0.001$ vs. toxin A^+; @ $P < 0.01$ vs. toxin A^+/5-ASA$^+$; & $P < 0.05$ vs. toxin A^+/4-APAA$^+$; && $P < 0.01$ vs. toxin A^+/4-APAA$^+$.

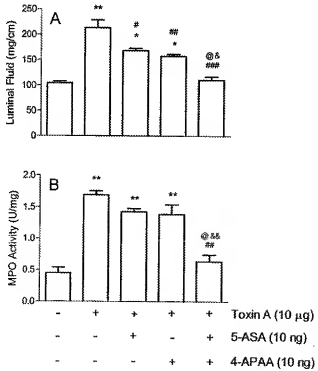


FIGURE 22

Clearly the figure is understandable in light of the description of the specific identifiers as set forth in the explanation of pages 6 and 7. Further Figures 10, 12, 14, 16, 18 and 20 use similar identifies along with descriptions of each figure in the section describing the figures. Thus, applicant would need to rewrite numerous sections. However, the application as written is clearly understandable. Applicants request that the Office reconsider this rejection.

List of copending and related applications

The only copending and related application to this series is U.S. Publication No. 2008-0033153 which applicants have included in the attached Supplemental IDS.

Verbose Specification

Applicants are very concerned that the Office finds the present application as verbose and points out page 30 of the specification as being particularly unclear. Notably that specific page is discussing results of testing and the different types of necrosis, as shown below. Applicants believe that such discussion is necessary for explaining the results and did not find the explanation as confusing or unclear. Applicants are not aware of any rules that limit how they explain their invention as long as the explanation is clear to one skilled in the art. Applicants have enablement requirements that often include long and rather complicated explanation of test results. If such a description is not included, a 112 rejection is experienced by applicants. Applicants request reconsideration of this request that the application needs to be rewritten because of verboseness.

diagnosed). In all sections from DNBS-treated rats, the serosa and adjoining mesentery were expanded by mild to moderately severe fibrovascular proliferation (early granulation tissue). Sections from two rats (#4 and #11, Mixture of 5-ASA and 4-APAA group), each contained a single, short, sharply demarcated segment of non-necrotic, non-ulcerated mucosa. Changes within these comparatively unaffected mucosal segments were limited to minimal to mild crypt epithelial hyperplasia, minimal crypt dilation, and minimal neutrophilic infiltration.

Severity scoring of colonic necrosis was based upon the degree of tissue involvement, however, grade 5 (severe) was reserved for lesions in which necrosis resulted in extensive tissue loss. Because the pattern of necrosis often varied from section to section, the individual intestinal layers were scored separately. Generally, the average severity scores for necrosis were comparable among the four groups of DNBS-treated rats, shown in the following table:

Group	SHAM	DNBS	5-ASA	4-APAA	Mixture 5-ASA & 4-APAA
No. Animals	(6)	(5)	(6)	(6)	(4)
Mucosa	0.00	4.20	4.50	4.33	3.50
Submucosa	0.00	4.20	4.17	4.00	4.25
Muscularis	0.00	3.60	3.5	3.17	3.00
Adventitia	0.00	1.40	1.67	1.67	1.50

The average score for mucosal necrosis in the Mixture of 5-ASA and 4-APAA group was lower than scores in the other groups of DNBS-treated rats due to the spared areas of mucosa in two animals from the Mixture of 5-ASA and 4-APAA group.

The principal histomorphologic changes observed in the colon sections of all rats treated with DNBS (regardless of any additional treatment) was partial to full-thickness, full-length, coagulative-type necrosis. Associated changes included massive bacterial invasion of the necrotic tissue, fibrinoid necrotizing vasculitis with thrombosis and hemorrhage, and heavy neutrophilic infiltration. Necrosis was not observed in the saline/methylcellulose-treated rats (SHAM group). The severity (extent) of necrosis was comparable among the four groups of DNBS-treated rats (DNBS, 5-ASA, 4-APAA, and Mixture of 5-ASA and 4-APAA), except that single segments of mucosa were comparatively spared in 2/4 rats from the Mixture of 5-ASA and 4-APAA group.

Anti-Inflammatory Activity of Drug Mixture

Dinitrobenzene sulfonic acid (DNBS) colitis was induced (no ether anesthesia) in 4 groups of 6 Lewis rats each. One DNBS group was dosed with vehicle (0.7% methyl cellulose) as well

Rejection of Claims and Traversal Thereof

In the June 10, 2009 Office Action,

Claims 15-30 and 32 were rejected under 35 U.S.C. §112, second paragraph; and

Claims 1-9, 15-30 and 32 were rejected under 35 U.S.C. §112, first paragraph; and

Applicants traverse these rejections and insist that none of the cited references alone or in combination defeat the patentability of the presently claimed invention which.

Rejection under 35 U.S.C. §112, second paragraph

Claims 15-30 and 32 were rejected under 35 U.S.C. §112, second paragraph. Applicants have amended claim 15, which is now much clearer as shown below:

> 15. (Currently amended) A pharmaceutical composition comprising at least a first and second therapeutic agent,
>
> wherein the first therapeutic agent is formulated to release in the stomach or small intestine and selected from the group consisting of
> azo-bonded 4-APAA compound;
> non-azo bonded 4-APAA compound;
> azo-bonded 5-ASA compound; and
> non-azo bonded 5-ASA compound; and
>
> wherein the second therapeutic agent is formulated to release in the distal portion of the small intestine or colon and selected from the group consisting of:
> 4-APAA compound azo bonded to a 5-ASA compound; and
> a combination of 4-APAA compound and a 5-ASA compound.

Clearly, the composition of claim 15 comprises at least two therapeutic agents and the selection for each agent is provided. Support for this claim and all claims depending therefrom, that being, new claims 33 to 40 can be found in the table as set forth on pages 21 and 22, and recreated below.

No.	Stomach	Small Intestine	Distal Small Intestine	Colon
1	5-ASA compound	None	5-ASA compound and 4-APAA compound	5-ASA compound and 4-APAA compound
2	5-ASA compound	5-ASA compound	5-ASA compound and 4-APAA compound	5-ASA compound and 4-APAA compound
3	5-ASA compound	None	None	5-ASA compound and 4-APAA compound
4	5-ASA compound	5-ASA compound	None	5-ASA compound and 4-APAA compound
5	4-APAA compound	None	5-ASA compound and 4-APAA compound	5-ASA compound and 4-APAA compound
6	4-APAA compound	4-APAA compound	5-ASA compound and 4-APAA compound	5-ASA compound and 4-APAA compound
7	4-APAA compound	None	None	5-ASA compound and 4-APAA compound
8	4-APAA compound	4-APAA compound	None	5-ASA compound and 4-APAA compound
9	None	None	5-ASA compound and 4-APAA compound	5-ASA compound and 4-APAA compound
10	None	5-ASA compound	5-ASA compound and 4-APAA compound	5-ASA compound and 4-APAA compound
11	None	None	None	5-ASA compound and 4-APAA compound
12	None	5-ASA compound	None	5-ASA compound and 4-APAA compound
13	None	None	5-ASA compound and 4-APAA compound	5-ASA compound and 4-APAA compound
14	None	4-APAA compound	5-ASA compound and 4-APAA compound	5-ASA compound and 4-APAA compound
15	None	None	None	5-ASA compound and 4-APAA compound
15	None	4-APAA compound	None	5-ASA compound and 4-APAA compound

[0096] Preferred components for compositions for oral administration for delivery of the therapeutic agent to a disease site in the small intestine or colon include the following: one or a combination of components selected from the group consisting of: AZO-bonded coatings, enteric coatings, pH sensitive coatings, coatings that dissolve in a pH range of about 5.5 to about 7, methacryllic polymers, time release coatings, microcapsules, biodegradable coatings, and redux sensitive coatings.

Clearly in light of the above table, and the discussion set forth in the application, there is sufficient support for the amendment to claim 15. Further, on page 18, there is a discussion regarding combinations and a table showing the possible combinations of azo bonded and non-azo bonded compounds.

The 4-APAA compound can be administered as a monotherapy. Alternatively, the 4-APAA compound can be administered as a component of a combination therapy regimen employing at least one 4-APAA compound and one or more other compounds. Where a combination therapy is used, the various therapeutic compounds can be administered separately or together as components of a single formulation.

Applicants request that the Office reconsider this amendment which is similar to originally filed claim 15 but much clearer.

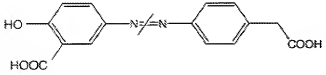
Rejection under 35 U.S.C. §112, first paragraph

Claims 1-9, 15-30 and 32 were rejected under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. Applicants disagree.

Claim 1 has been amended, thereby obviating this rejection. Further support for the combination is set forth above.

According to the Office, the specification does not include sufficient disclosure for the claim limitation that recites "a 4-APAA compound azo bonded to a 5-ASA compound for release in the colon." Applicants disagree.

There are numerous sections of the specification that discusses the use of the APAZA compound (a 4-APAA compound azo bonded to a 5-ASA compound) for release in the colon. Notably, the structure of APAZA is shown below:



Clearly this compound is a 4-APAA compound azo bonded to a 5-ASA compound as shown below and recreated from page 40:

Inhibition of *Clostridium difficile* toxin A-induced colitis in rats by APAZA™ and 4-APAA

The APAZA™ compound [molecule of 5-aminosalicylic acid (5-ASA) linked to one molecule of 4-aminophenylacetic acid (4-APAA) by an azo bond] was tested for its ability to inhibit acute colitis in rats caused by *Clostridium difficile* toxin A. When administered

Support that this 4-APAA compound azo bonded to a 5-ASA compound is released in the colon of an animal can be found in at page 42 and recreated below:

Results. The effects of chronic treatment with APAZA™ on toxin A-induced structural damage of the colon as assessed by H&E staining of fixed tissue is shown in Figure 8. APAZA™ administered in the drinking water at all three doses (1, 10, and 100 mg/kg·day) strongly protected the structural integrity of the rat colon against the damaging effects of toxin A. The degree of protection afforded by APAZA™ appeared to be virtually complete at all three doses so there was little evidence of a dose-related effect. In addition, there was little variability among the several histological preparations for the effects of APAZA™ unlike what was observed for the highest dose of sulfasalazine described below.

Thus, one skilled in the art would recognize that applicants were in possession of the presently claimed invention.

The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. Notably, it is well settled in the law that examples are not required for each embodiment of the claimed invention. As explained in *LizardTech, Inc. v. Earth Resource Mapping, PTY, Inc.*:

> "A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before. Placed in that context, it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention . . . . "

424 F.3d 1336, 1345 (Fed. Cir. 2005) (citing Union Oil Co. v. Atl. Richfield Co., 208 F.3d 989, 997 (Fed. Cir. 2000); In re GPAC Inc., 57 F.3d 1573, 1579 (Fed. Cir. 1995)).

The Office bears the initial burden of presenting a *prima facie* case of unpatentability. *In re Oetiker*, 24 USPQ2d 1443 (Fed. Cir. 1992). Insofar as the written description requirement is concerned, that burden is discharged by "presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined in the claims." *In re Wetheim*, 191 USPQ 90, (C.C.P.A. 1976). In the present situation, the specification contains a description of the claimed invention, as shown above, and thus the Office, in order to meet the burden of proof, must provide reasons why one of ordinary skill in the art would not consider the description sufficient. *In re Alton*, 37 USPQ2d 1578 (Fed. Cir. 1996). The Office has not met this burden.

Accordingly, applicants request the withdrawal of this rejection under section 112, first paragraph.

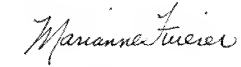
Fees Payable

No fee is due for entry of this amendment but in the event any fee is found due, the U.S. Patent and Trademark Office is hereby authorized to charge any additional amount necessary to the entry of this amendment to Deposit Account No. 13-4365 of Moore & Van Allen PLLC.

Conclusion

Applicants have satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Spivack reconsider the patentability of the pending claims in light of the distinguishing remarks herein, and withdraw all rejections, thereby placing the application in condition for allowance. If any issues remain outstanding incident to the allowance of the application, Examiner Spivack is requested to contact the undersigned attorney at (919) 286-8089.

Respectfully submitted,



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